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ORIGINAL ARTICLE

Early detection of premature subclinical coronary atherosclerosis in systemic lupus erythematosus patients

Khaled Mohamed Said Othman [a,*], **Naglaa Youssef Assaf** [b]

[a] *Department of Cardiology, Ain Shams University, Faculty of Medicine, Egypt*
[b] *Department of Physical Medicine, Rheumatology & Rehabilitation, Ain Shams University, Faculty of Medicine, Egypt*

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KEYWORDS

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Abstract *Objective:* To elucidate early coronary atherosclerotic changes in premenopausal systemic lupus erythematosus (SLE) female patients without clinical cardiovascular manifestation using a 64-slice Multi-detector computed tomography (MDCT) scan to detect coronary calcification and measure coronary calcium score (CCS), and to find out its correlation to some traditional and non-traditional risk factors.

Methodology: Sixty consecutive premenopausal SLE female patients, and sixty age and sex matched healthy subjects without known systemic, immunological, or cardiovascular disease (served as a control group) underwent clinical examination, serological analysis, and 64-slice MDCT-based coronary calcium scoring. All the clinical, serological, and MDCT parameters of the patients were correlated.

Results: Coronary calcification (CC) was seen in 21 patients (35%), the number of atherosclerotic calcified plaques ranged from 0 to 19. Calcium scores ranged from 0 to 843. In contrast to control subjects, SLE patients had significantly higher erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), total cholesterol level, low-density lipoprotein (LDL), immunoglobulin G (IgG) and IgM anti-cardiolipin antibodies, serum intracellular adhesion molecule (sICAM) and E-selectin levels. SLE patients had highly significantly more atherosclerotic plaques (3 ± 0.66 compared to 0.1 ± 0.07, $p < 0.001$) and higher CCS (59.2 ± 20.3 compared to 2.6 ± 1.85, $p < 0.001$). Significant positive correlation was found between both number of atherosclerotic plaques and CCS

* Corresponding author.
E-mail addresses: drkh.m.saeed@me.com, kh_m_saeed@yahoo.com (K.M.S. Othman).

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and total cholesterol level, LDL, cumulative prednisone dose, SLE disease activity index (SLEDAI), ESR, CRP, sICAM-1, E-Selectin, and anti-cardiolipin antibodies ($p < 0.05$ in all).

Conclusion: Pre-menopausal SLE female patients free from clinical atherosclerotic vascular disease have an increased number of atherosclerotic plaques and CCS, which correlate positively with SLEDAI disease activity score, serum CRP, anticardiolipin antibodies, sICAM-1, E-Selectin, LDL level, total cholesterol level, and cumulative prednisone dose. In addition, we conclude that MDCT is a non-invasive, sensitive, reproducible, and reliable tool for accurate measurement of coronary calcification.

1. Introduction

Systemic lupus erythematosus (SLE) is a systemic inflammatory disease that affects primarily women and causes chronic vascular inflammation.[1] Women with SLE have a high frequency of coronary artery disease (CAD) and exhibit high rates of myocardial infarction that are up to 52 times higher than in women without SLE in the age between 35 and 44 years.[2] As treatments for lupus itself have generally improved, direct mortality rates have declined and cardiovascular co-morbidities have become a growing clinical problem. Circulatory diseases are today a leading cause of mortality among SLE patients.[3] Several studies of subclinical atherosclerosis have identified that 30–40% of women with SLE have myocardial perfusion abnormalities.[4–6]

There has been a growing interest in the hypothesis that atherosclerosis may be an immune-inflammatory disease; in this regard, SLE is an interesting model because it represents an inflammatory disease of autoimmune origin.[7]

The mechanism of accelerated atherosclerosis in SLE is not clear. Several factors have been implicated for the high prevalence of premature CAD; these factors are a mixture between traditional risk factors and factors associated with the disease itself or its treatment. SLE patients have increased prevalence of conventional risk factors like hypercholesterolemia, diabetes mellitus, obesity, hypertension, and sedentary life.[8] Risk factors related to SLE and its treatment include the presence of anti-phospholipid antibodies like anti-cardiolipin antibodies (aCL), which are considered as an independent risk factor for myocardial infarction,[9] corticosteroid therapy either due to their direct atherogenic effects or through enhancement of traditional risk factors such as hyperlipidemia, hyperglycemia, hypertension, and obesity.[10,11] Also having SLE is considered an independent risk factor for cardiovascular disease[2]; the ongoing inflammatory process accompanying multiple immunological and procoagulant abnormalities in SLE[12], and the underlying genetic susceptibility to develop accelerated atherosclerosis in patients with SLE may play a role.[13]

Coronary calcium is closely associated with the presence and extent of atherosclerotic plaque and therefore constitutes a potential marker for early stages of coronary atherosclerosis in asymptomatic subjects.[14]

Therefore, this study was planned to elucidate early coronary atherosclerotic changes in premenopausal SLE female patients without clinical cardiovascular manifestation, using a 64-slice MDCT scan to detect coronary calcification and measure coronary calcium score, and to find out its correlation to some traditional and non-traditional risk factors.

2. Patients and methods

Between June 2010 and April 2012, sixty consecutive premenopausal SLE female patients fulfilling the criteria of the American College of Rheumatology (ACR) for the classification of SLE[15] were studied. We included only premenopausal women in order to avoid the strong confounding effect of low estrogen levels on the risk of vascular disease. We excluded patients with juvenile onset SLE; patients with other connective tissue diseases; clinical atherosclerotic vascular disease (previous cardiac, cerebral, or peripheral vascular affection); family history of premature CAD; diabetes mellitus; arterial hypertension; current smoking habit; or birth control using oral contraceptive pills so that we can limit the causes of early atherosclerotic changes in premenopausal female patients to the effect of SLE and/or its therapy. A group of sixty healthy female subjects of matched age (age is a known strong predictor of atherosclerosis) without known systemic, immunological, or atherosclerotic vascular disease served as a control group. The Royal Commission Hospital Ethics and Research Committee approved the study on March 2010.

At the time of the study, detailed disease and medication history (steroid intake duration, dosage, and frequency); calculation of body mass index (BMI) according to the following equation: BMI = Body weight in kg/Height in m.^{2} assessment of disease activity using the SLE Disease Activity Index (SLEDAI) according to Bombardier et al. (1992)[16]; laboratory assessment of complete blood count (CBC) using Coulter Counter T660, erythrocyte sedimentation rate (ESR) using the Westergren method, C-reactive protein (CRP) using the ELISA technique, antinuclear antibodies (ANA) by indirect immune-florescence using Kallestad kit, anti-double stranded DNA by the indirect immune-fluorescence technique, anti-cardiolipin antibodies (IgG and IgM) by enzyme linked immunosorbent assay (ELISA) according to Harris et al. (1987),[17] and 12 h fasting lipid profile (including total cholesterol, triglycerides, LDL-cholesterol, and HDL-cholesterol) using CX5 system (Beckman US) were performed.

2.1. Coronary calcium scoring protocol

Patients were scanned using a 64-slice CT scanner (General Electrics LightSpeed VCT, Milwaukee, WI, USA). A non-enhanced low-dose ECG-gated scan covering the whole heart during a single breath hold was performed at 70–75% of the R–R interval using the following scan parameters: detector coverage 1.25 mm; gantry rotation time 350 ms; tube voltage 120 kV; and tube current 180–200 mA. Datasets were reconstructed from the retrospectively gated raw data. Images were

reconstructed with an effective slice thickness of 2.5 mm. Coronary arteries were evaluated using the reconstruction dataset with the least motion artifacts, typically an end-diastolic phase. The effective dose of the CS scans was estimated from the dose-length product and an organ weighting factor [$k = 0.014$ mSv X (mGy X cm)$^{-1}$] for the chest as the investigated anatomical region.[18] For data analysis post-processing of the CS examinations was performed on dedicated workstations (Vitrea2, Vital Images, USA and Advantage, GE Healthcare, USA). The CS was calculated using the Agatston method.[19] All scans were interpreted by the same cardiologist who was unaware of the subjects' clinical status at the time of interpretation. Coronary calcium was assumed to be present if a computed tomography attenuation value of at least 130 Hounsfield units (HU) was found in two or more adjacent pixels which could be assigned to the coronary artery system. Semi automated software was used to calculate the "Agatston score" after manual identification of calcified lesions in the coronary arteries. Coronary artery calcium (CAC) score was categorized based on the published guidelines that corresponded to the probability of significant CHD: 0 (very low probability of CHD), 1–10 (very unlikely CHD), 11–100 (likely mild to minimal coronary stenosis), >100–400 (non-obstructive CHD), and >400 (high likelihood of >1 "significant" coronary stenosis) with a very high risk for future events due to coronary artery disease.[20]

2.2. Statistical analysis

Data were collected, tabulated, and analyzed using the scientific package of social statistics program. The mean and standard deviation were determined and the statistical significance was calculated using Student's "*t*" test for paired data. The Mann–Whitney (*U*) test using standard error of the mean to calculate *z* was used for comparison of the coronary calcification parameters. The Chi square test was used to compare the probability of having CHD based on coronary calcium score categorization. A value of $p < 0.05$ was considered statistically significant. Correlation coefficient "*r*" for the relationship of different variables was calculated using Pearson's coefficient for quantitative data and spearman correlation for qualitative (non-parametric) data.

3. Results

This cross sectional observational study was carried out on 60 consecutive premenopausal SLE female patients and 60 controls during the period from 06/2010 to 4/2012.

3.1. Demographic and clinical characteristics of control group

A group of 60 healthy female subjects, ranged in age from 18 to 41 years with a mean of 31.7 ± 5.9 years served as a control group. None of them was known to have previous or current systemic, immunological, or atherosclerotic vascular disease. Demographic data, clinical, laboratory, number of atherosclerotic plaques and CCS of controls are summarized in Table 1.

Coronary calcification (CC) was seen in two subjects (3.3%) of the control group, the number of atherosclerotic calcified plaques ranged from 0 to 3 (mean 0.1 ± 0.07), Calcium scores ranged from 0 to 83 (mean 2.6 ± 1.85) (Table 2).

3.2. Demographic and clinical characteristics of patients

This study included sixty consecutive premenopausal SLE patients ranged in age from 18 to 40 years with a mean of 31.4 ± 6 years. All of them were diagnosed as having SLE based on the criteria of the American College of Rheumatology for the classification of SLE.[13] The disease duration ran-

Table 1 Comparison between patients and control regarding demographic data, clinical, laboratory, and MDCT results.

Parameter	SLE (No = 60)		Controls (No = 60)		*T*-test	
	Mean	SD	Mean	SD	*t*	*p*-Value
Age	31.40	6.00	31.70	5.90	0.28	($p > 0.05$) NS
BMI	26.00	4.90	25.70	3.90	0.37	($p > 0.05$) NS
SSBP	121.00	9.80	119.00	18.00	0.76	($p > 0.05$) NS
SDBP	82.60	3.80	80.00	6.00	0.84	($p > 0.05$) NS
ESR	69.70	27.00	12.10	5.00	16.48	($p < 0.001$) HS
CRP	23.00	4.90	5.00	2.00	26.35	($p < 0.001$) HS
Total cholesterol	212.90	43.60	179.20	23.40	5.27	($p < 0.05$) S
LDL cholesterol	139.80	23.20	102.30	21.20	9.24	($p < 0.05$) S
HDL cholesterol	46.74	18.40	56.34	14.10	3.21	($p < 0.05$) S
Triglycerides	118.19	30.10	113.17	21.40	1.05	($p > 0.05$) NS
IgG aCL (GPL units/ml)	25.90	12.60	10.84	5.80	21.76	($p < 0.001$) HS
IgM aCL (MPL units/ml)	13.15	3.76	4.14	2.90	25.45	($p < 0.001$) HS
sICAM	289.20	66.20	201.10	19.40	9.89	($p < 0.05$) S
E-Selectin	72.30	9.60	43.20	2.20	8.92	($p < 0.05$) S
Number of atherosclerotic plaques	3	0.66*	0.1	0.07*	4.46**	($p < 0.001$) HS
CCS	59.2	20.3*	2.6	1.85*	4.38**	($p < 0.001$) HS

BMI = body mass index, SSBP = sitting systolic blood pressure, SDBP = sitting diastolic blood pressure, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, LDL = low density lipoprotein, HDL = high density lipoprotein, aCL = Anti-cardiolipin antibodies, sICAM-1 = soluble intercellular adhesion molecule-1, MDCT = Multi detector CT, CCS = coronary calcium score.

* Standard error of the mean.

** *z* Value.

Table 2 Distribution of coronary calcification in SLE patients and controls.

Coronary arteries	Patients: No. (%)	Control: No. (%)
LAD	8 (38.1%)	1 (50%)
Lt CX	2 (9.5%)	0
RCA	4 (19.0%)	0
LAD + Lt CX	1(4.8%)	0
LAD + RCA	3(14.3%)	1 (50%)
Lt CX + RCA	0	0
LAD + Lt CX + RCA	3 (14.3%)	0
Total	21 (100%)	2 (100%)

LAD = left anterior descending artery, Lt CX = left circumflex, RCA = right coronary artery.

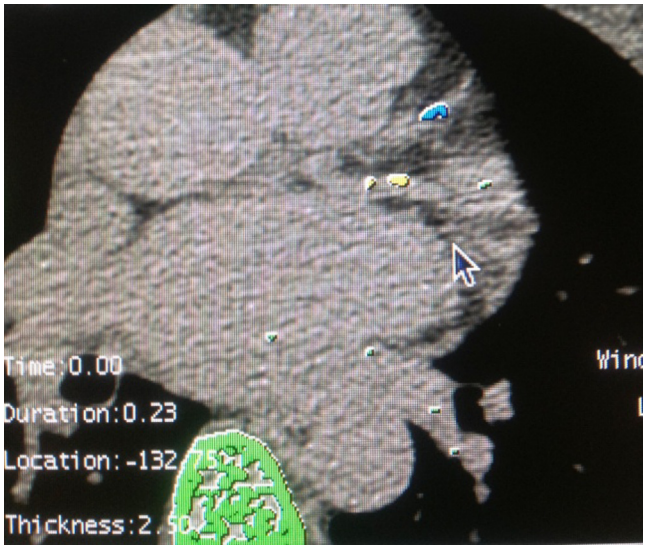

Figure 1 Example of MDCT in SLE patient, one calcified plaque is seen in the left anterior descending artery (blue color) and two calcified plaques in the circumflex artery (yellow color).

ged from 0.1 to 10 years with a mean of 5.1 ± 2.8 years. All of them had no clinical atherosclerotic vascular manifestations on examination. Demographic data, clinical, laboratory, number of atherosclerotic plaques and **CCS** of patients are summarized in Table 1.

Coronary calcification (CC) was seen in 21 patients (35%), the number of atherosclerotic calcified plaques ranged from 0 to 19 (mean 3 ± 0.66), calcium scores ranged from 0 to 843 (mean 59.2 ± 20.3) (Table 2).

Sub-group analysis for the distribution of coronary calcification according to the coronary artery/s affected in both SLE patients and control subjects is shown in Table 2, Figs. 1 and 2. Further categorization of CAC score in both SLE patients and controls based on the probability of significant coronary heart disease (CHD) is shown in Table 3.

At the time of the study, all patients received prednisone regularly, with a mean dose of 25 mg/day and a cumulative dose of 32 ± 11.6 g.

SLE patients had significantly higher ESR, CRP, total cholesterol, and LDL levels; significantly lower HDL levels; and significantly higher IgG aCL, IgM aCL, sICAM, and E-Selectin levels. SLE patients had highly significantly more atherosclerotic plaques and higher CCS. On the other hand, no statistically significant differences were detected between patients and control regarding the age, BMI, systolic and diastolic blood pressure, or triglyceride levels (Table 1).

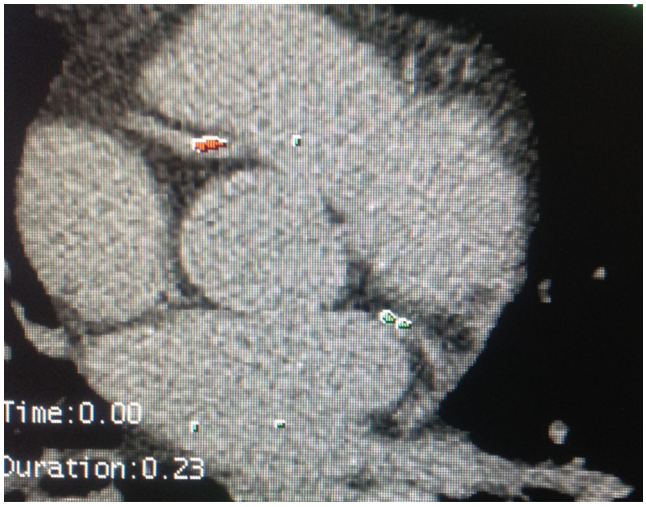

Figure 2 Example of MDCT in SLE patient, one calcified plaque is seen in the right coronary artery (red color).

The probability of having CAD was significantly higher in SLE patients in comparison to control as only 65% of the SLE patients had zero CCS (very low probability of CHD) in comparison to 96.7% of the control $p < 0.000$. Twenty percentage of the SLE patients had CCS from 11–100 (likely mild to minimal coronary stenosis) in comparison to only 3.3% of the control subjects $p < 0.001$. Moreover the probability of having significant CAD was higher in SLE patients in comparison to control, 10% of the SLE patients had CCS of >100–400 (non-obstructive CHD) and 5% of the SLE patients had CCS of > 400 (high likelihood of significant coronary stenosis) while no subjects in the control group had CCS >100 with a highly significant p value < 0.001 in both (Table 3).

On studying the correlation between the various data of the SLE patients, using *Pearson's correlation coefficient* we found significant positive correlation between both number of atherosclerotic plaques and CCS and total cholesterol level, LDL level, cumulative prednisone dose, SLEDAI disease activity score, ESR, CRP, sICAM-1, E-Selectin, and anti-cardiolipin antibodies ($p < 0.05$ in all). Significant negative correlation was also found between number of atherosclerotic plaques and CCS and HDL. On the other hand no significant fixed correlation was found between number of atherosclerotic plaques and CCS and any of patients' age, disease duration, body mass index, SSBP, SDBP, and serum triglyceride level (Table 4).

4. Discussion

There has been a growing interest in the hypothesis that atherosclerosis may be an immune-inflammatory disease; in this regard, SLE is an interesting model of atherosclerosis because it represents an inflammatory disease of autoimmune origin.[7] Compared with women in the general population, women with

Table 3 Coronary calcium score categorization in SLE patients and controls.

Coronary calcium score	Patients: No. (%)	Control: No. (%)
0 (very low probability of CHD)	39 (65%)	58 (96.7%)
1–10 (very unlikely CHD)	3 (5%)	0
11–100 (likely mild to minimal coronary stenosis)	12 (20%)	2 (3.3%)
>100–400 (non-obstructive CHD)	4 (10%)	0
>400(high likelihood of "significant" coronary stenosis)	2 (5%)	0
Total	60 (100%)	60 (100%)

Table 4 Correlation between number of atherosclerotic plaques and CCS and demographic, clinical, and laboratory results in SLE patients.

Parameter	Number of atherosclerotic plaques		CCS	
	r	*p*	*r*	*p*
Age (years)	0.19	.066	0.20	.060
Disease duration (years)	0.10	.080	0.21	.065
BMI (kg/m^2)	−0.12	.075	0.08	.570
SSBP (mm Hg)	0.06	.650	0.22	.061
SDBP (mm Hg)	0.09	.075	0.07	.600
ESR (mm/1st hour)	0.26	.045	0.28	.040
CRP (mg/l)	0.35	.010	0.33	.020
Total cholesterol (mg/dl)	0.39	.008	0.43	.003
LDL cholesterol (mg/dl)	0.46	.001	0.51	.000
HDL cholesterol (mg/dl)	−0.42	.003	−0.59	.000
Triglycerides (mg/dl)	0.06	.700	0.03	.785
IgG aCL	0.29	.038	0.25	.050
IgM aCL	0.24	.048	0.27	.043
sICAM (ng/ml)	0.26	.041	0.28	.040
E-Selectin (ng/ml)	0.25	.038	0.31	.022
SLEDAI	0.29	.035	0.37	.009
Cumulative prednisone level (gm)	0.31	.022	0.38	.008

BMI = body mass index, SSBP = sitting systolic blood pressure, SDBP = sitting diastolic blood pressure, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, LDL = low-density lipoprotein, HDL = high-density lipoprotein, aCL = Anti-cardiolipin antibodies, sICAM-1 = soluble intercellular adhesion molecule-1, SLEDAI = systemic lupus disease activity index, CCS = coronary calcium score.

SLE have been found to be more likely to develop CHD, with this risk being particularly marked in women younger than age 55 years.[21] The risk of a CVE, or MI, was eight- or ninefold greater among middle-aged female SLE patients.[22] Doyle et al., 2009, reported a case of acute myocardial infarction due to coronary artery thrombosis as the presenting manifestation of SLE in a 12 year old female child.[23]

Coronary calcium deposits provide an independent prediction of short and long-term cardiac events. Even in patients with normal SPECT results, the increased coronary calcium score identifies subjects at high long-term cardiac risk.[24] MDCT is characterized by very high specificity (95–97%) and excellent negative predictive value (93–99%) for stable coronary artery disease diagnosis.[25] Coronary calcification detected by MDCT independently predicts CVS events in patients with RA and SLE. Risk stratification by assessment of CCS may have an important role in patients with systemic inflammatory disease.[26] Thus; an early stage of coronary artery disease may be diagnosed in patients with atherosclerotic plaques detected by MDCT.

This study was designed to elucidate early preclinical atherosclerotic changes in premenopausal SLE female patients using a 64-slice MDCT scan to detect coronary calcification and measure coronary calcium score as a non-invasive, sensitive, and reproducible screening tool for the detection of subclinical coronary affection in SLE patients, and to study their correlation to some traditional and non traditional CAD risk factors for possible implementation of preventive measures and initiation of therapy early in the course of the disease.

Our results showed that coronary atherosclerotic lesions (CC) were seen in 21 premenopausal SLE patients without clinically overt atherosclerotic vascular disease (35%), highly significant differences between patients and control regarding the number of atherosclerotic plaques and CCS ($p < 0.001$ in both) were also detected.

These findings reflecting higher incidence of subclinical atherosclerosis in premenopausal SLE female patients can be explained by the contribution of SLE with its systemic nature to atherosclerosis by more than one mechanism. Early immune system dys-regulation and altered complement metabolism may reduce arterial elasticity, creating an atherogenic milieu; changes in the geometric configuration of vessels may lead to smooth muscle cell proliferation and increased collagen deposition; the intimal layer of these stiffened vessels then becomes vulnerable to atherosclerosis with increased lipoprotein, albumin, and leukocyte permeability. Thus, an early effect of

SLE with vascular stiffening may set the stage for an acceleration of the atherosclerotic process through traditional risk factors.[27] In addition, the inflammatory process associated with SLE may affect the vessel wall thickness and the development of plaque. It is now generally believed that inflammation plays an integral role in atherogenesis, and that prolonged exposure to even low levels of acute-phase reactants may cause vascular injury leading to cardiovascular disease.[28]

Our results are in agreement with earlier studies done by Kao et al., 2008, in the first study to compare the prevalence of coronary artery calcification among non-diabetic and age-matched female patients with SLE, RA, and healthy controls who found that in young subjects with the mean age of 40, the frequency of coronary artery calcifications is 30–40%.[29] In addition, in a study done by Yiu and his colleagues in 2009, who studied 50 SLE patients and found that the frequency of atherosclerotic plaques observed in MDCT was highest in coronary arteries (42%) of patients with calcifications.[30] Recent studies showed that 25% of asymptomatic SLE patients manifested with atherosclerosis in coronary arteries[31] and CAC was present in 17% of SLE patients.[32]

On studying the correlation between the various data of the SLE patients, we found significant positive correlation between both number of atherosclerotic plaques and CCS and total cholesterol level, LDL level, cumulative prednisone dose, SLE-DAI disease activity score, ESR, CRP, sICAM-1, E-Selectin, and anti-cardiolipin antibodies ($p < 0.05$ in all). Significant negative correlation was also found between number of atherosclerotic plaques and CCS and HDL. On the other hand no significant fixed correlation was found between number of atherosclerotic plaques and CCS and any of patients' age, disease duration, body mass index, SSBP, SDBP, and serum triglyceride level.

Increased risk of coronary artery calcification in SLE patients with higher levels of CRP can be explained by the inflammatory microenvironment in SLE that promotes the formation of oxidized LDL which is responsible for the oxidative injury of vascular wall.[33] CRP induces the expression of adhesion molecules on the endothelial surface (including vascular cell adhesion molecule-I, intercellular adhesion molecule-I, and E-selectin) and promotes the adherence of leucocytes with the resultant initiation of vascular atherosclerotic damage.[34] CRP in particular has been emerging as a strong predictor of CAD outcomes.[35] Prolonged exposure to even low levels of acute-phase reactants may cause vascular injury leading to cardiovascular disease.[1]

Our results are in agreement with Kao et al., 2008, who showed that coronary artery calcification in female patients with SLE may be linked to CRP and he reported that this is consistent with the exceedingly high risk of myocardial infarction in young women with SLE independent of traditional CHD risk factors. Their study also supports the notion that inflammation and endothelial activation may play the most significant roles in accounting for this excess risk.[29] Pons-Estel et al., 2009, showed that SLE patients with CRP levels > 20 mg/l were at increased risk of cardiovascular damage.[36]

On the other hand, the study of Plazak and his colleagues in 2011, did not show an influence of hyperlipidemia on coronary calcification formation or myocardial perfusion defects in SLE patients. Moreover, they reported that a generalized inflammation reflected by higher CRP did not significantly resulted in the presence of atherosclerotic lesions. They explained their results by the lack of subjects with severely augmented inflammatory process in their study.[31]

The conventional risk factors for coronary artery disease (increased total cholesterol and LDL) in our study, cannot alone explain the increased risk of atherosclerosis and cardiovascular complications in SLE patients. The other possible mechanisms include a generalized, chronic inflammation, reflected by high C-reactive protein level.[36] Besides the chronic inflammation, the second factor that may potentially influence pathologic changes in the arteries is the presence of antiphospholipid antibodies.[37]

Among the possible known mechanisms for the role of antiphospholipid antibody mediated vascular injury is the enhancement of the expression of ICAM-1, VCAM-1, and E-selectin on endothelial cells (ECs) and that these effects are correlated with increased adhesion of leukocytes to endothelium. Activation of ECs by antiphospholipid antibody (aPL) may create a hypercoagulable state that precedes and contributes to thrombosis in SLE patients.[37] In addition, Lima et al., 2002, reported that it is possible that in the subgroup of SLE patients with positive aPL, the smooth muscle cell proliferation takes place earlier than in the SLE group without aPL.[10] It is of interest to note that antibodies against cardiolipin were predictive of MI in SLE patients approximately one decade earlier than antibodies against ox LDL. Thus, individuals with antibodies against cardiolipin seem to have a more unfavorable outcome of the disease.[38] Vaarala et al., 1995, in a prospective cohort of healthy middle-aged men concluded that, aCL level is considered an independent risk factor for myocardial infarction.[9] In SLE patients, CAD has been correlated with aCL and anti-oxidized LDL antibodies.[39] These findings along with increased lipid peroxidation in aCL positive SLE patients suggest that the presence of these antibodies can be associated with subclinical atherosclerosis in SLE patients.[40]

Our results are in agreement with Rho et al., 2009, who concluded that the adhesion molecules VCAM, ICAM, and E-selectin, and the cytokine TNF-α are associated with coronary atherosclerosis independent of the conventional risk factors.[41] They studied a population with asymptomatic, subclinical atherosclerosis, and their findings suggest that adhesion molecules and TNF-α may contribute at a relatively early stage of atherosclerotic vascular disease in this population and therefore may represent a potential target for the prevention of subsequent symptomatic atherosclerosis in patients with SLE.

Gustafsson et al., 2009, in their prospective study to investigate lupus associated CAD risk factors for the first ever cardiovascular event (CVE) in patients with SLE reported that positive aPL, and biomarkers indicating increased endothelial cell activity are independent predictors of CVEs.[3] Their results indicate that activation of the endothelium and the coagulation system are important features in SLE related CVD. Furthermore, they observed that the risk of CVEs seems to increase in SLE patients with positive aPL, elevated von Willebrand factor (vWf), and soluble VCAM1.[3]

Plazak et al., 2011, showed an association of coronary calcification formation in SLE patients with the presence of antiphospholipid antibodies.[31] Various studies have suggested that antiphospholipid antibodies may cause thrombosis by activation of endothelial cells or platelets or by inhibition of the pro-

tein C activation pathway.[37]The antiphospholipid antibodies may also initiate or exacerbate the process of lipid deposition and plaque formation.[42]

Assessment of disease activity score at the time of the scan cannot accurately reflect the level of lupus activity throughout the course of the disease. Average activity scores over a longer period may provide more accurate estimates of lupus activity and its relationship to atherosclerosis.[2]

Our study showed a significant positive correlation between both number of atherosclerotic plaques and CCS and the cumulative prednisone dose. This could be explained by direct atherogenic effects of steroids or through enhancement of traditional factors such as hyperlipidemia, hyperglycemia, hypertension, and obesity.[10] Alekberova et al., 2004, found an association between duration of use and cumulative doses of corticosteroid and plaque formation.[11,43] Doria et al., 2003, showed that in SLE patients the most important non-traditional risk factor for atherosclerosis was the cumulative corticosteroid dose.[7] Steroid treatment is often believed to be atherogenic due to the effect on plasma lipoproteins, but inflammation is implicated in atherosclerosis, so steroids could possibly prevent atherosclerosis as well. Clearly, the role of steroid treatment in development of arterial disease in SLE deserves further study.[11,44]

4.1. Study limitations

This study has an important limitation which is the cross sectional nature that may fail to estimate the true magnitude for the contribution of variables such as disease activity and therapy. A prospective study might demonstrate a greater effect over time.

5. Conclusion

This study demonstrated that pre-menopausal SLE female patients free from clinical atherosclerotic vascular disease have an increased number of atherosclerotic plaques and CCS, which correlates positively with SLEDAI disease activity score, serum CRP values, anticardiolipin antibody, sICAM-1, E-Selectin, LDL level, total cholesterol concentration, and cumulative prednisone dose. In addition, we conclude that MDCT is a non-invasive, sensitive, reproducible, and reliable tool for accurate measurement of coronary calcification, that indirectly reflects subclinical coronary affection, and it is considered a useful tool for the follow up of the course of atherosclerosis over time.

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